REMARKS / ARGUMENTS

Claims 1-9 were pending. However, claims 5, 7 and 9 have been cancelled and claims 10 and 11 have been added. Thus, claims 1-4, 6, 8, 10 and 11 are now pending and under consideration.

The allowance of claims 1, 6 and 8 is noted with sincere appreciation.

Claims 2, 3 and 4 have been amended by inserting the word "hemihydrate" after "3-Z-[1-(4-(N-((4-methyl-piperazin-1-yl)-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2- indolinone-monoethanesulphonate". This amendment was made because these claims are directed to a single species, a single crystalline form of 3-Z-[1-(4-(N-((4-methyl-piperazin-1-yl)-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2- indolinone-monoethanesulphonate hemihydrate. It is clear from the specification, at page 8, lines 6-10, that the crystalline form that is the subject of the invention is the hemihydrate. Claims 2, 3 and 4 differ only in that they characterize this one species using three different physical parameters (melting point, XRPD peaks and unit cell dimensions as determined mathematically from XRPD data). Other hydrated forms of 3-Z-[1-(4-(N-((4-methyl-piperazin-1-yl)-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2- indolinone-monoethanesulphonate (for example, the anhydrous form) would be distinct species which presumably would not assume crystalline forms that could be characterized in the manner set forth in these claims.

Claim 5 has been canceled because it is redundant with claims 2, 3 and 4 as amended.

Claims 2 to 5 have been rejected as being substantially duplicative of each other. Claim 5 has been canceled, making rejection of this claim moot. Rejection of claims 2, 3 and 4 on this basis is respectfully traversed. It is respectfully asserted that there is no statutory basis for such rejection. Should the Examiner disagree she is invited to set forth the supposed statutory basis.

Claim 7, which stands rejected, has been cancelled and replaced with new claim 10. Claim 10 is directed to a single metabolite of 3-Z-[1-(4-(N-((4-methyl-piperazin-1-yl)-

methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone-monoethanesulphonate. That single metabolite is 3-Z-[1-(4-(N-((4-methyl-piperazin-1-yl)-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-carboxy-2-indolinone. Moreover, claim 10 is directed to this single metabolite "in substantially pure form". Accordingly, claim 10 does not read on the impure product that would arise in vivo as a result of the administration of 3-Z-[1-(4-(N-((4-methyl-piperazin-1-yl)-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone-monoethanesulphonate. Support for new claim 10 is found in the specification at page 11, lines 6-16, which reads in part:

> Experimental studies have shown that a metabolite of the compound 3-Z-[1-(4-(N-((4-methyl-piperazin-1-yl)-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone-monoethanesulphonate is the de-esterified 3-Z-[1-(4-(N-((4-methyl-piperazin-1-yl)-carbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-carboxy-2-indolinone. The in-vitro inhibitory activity of this metabolite on several kinases has been evaluated, using standard known kinase inhibition assays as well as a standard known cellular proliferation inhibition assay (inhibition of the proliferation of Human Umbilical Cord Endothelial Cells stimulated by the VEGF, the so-called "HUVEC cellular assay"). These experimental results have shown that this metabolite inhibits several kinases, such as VEGFR-2, VEGFR-3, Her-2, FGFR-1, PDGFR-alpha or InsR, as well as the proliferation of HUVEC VEGF stimulated cells.

Admittedly, the above passage states that the de-esterified metabolite is 3-Z-[1-(4-(N-((4-methyl-piperazin-1-yl)-carbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-carboxy-2-indolinone. However, it will be clear to one of ordinary skill in the art that 3-Z-[1-(4-(N-((4-methyl-piperazin-1-yl)-**methyl**carbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone-monoethanesulphonate was intended because the starting material prior to de-esterification is 3-Z-[1-(4-(N-((4-methyl-piperazin-1-yl)-**methyl**carbonyl)-N-methyl-

amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone-monoethanesulphonate.

Moreover, the specification provides support for the production of this single metabolite in substantially pure form, by way of the reference at page 11, lines 3 and 4, to WO 01/27081, which describes how such compounds can be made synthetically.

The rejection of claim 9 is rendered moot by its cancellation.

New claim 11 is directed to 3-Z-[1-(4-(N-((4-methyl-piperazin-1-yl)-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2- indolinone-monoethanesulphonate hemihydrate in crystalline form. This claim is narrower than claim 1, which is directed to the compound regardless of crystalline state, but broader than claims 2, 3 and 4 which are limited not only to the crystalline state but to a particular crystalline form that is characterized by the physical properties recited in these claims.

Respectfully submitted,

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December 16, 2005
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